Antianginal Therapy Before Percutaneous Coronary Intervention

William B. Borden, MD; John A. Spertus, MD, MPH; Alvin I. Mushlin, MD, ScM; Matthew T. Roe, MD, MHS; Lisa A. McCoy, MS; Rita F. Redberg, MD, MSc

**Background**—The regional variability of percutaneous coronary intervention (PCI) rates may be explained by variations in the medical treatment of stable coronary artery disease. We sought to determine whether greater regional use of antiangial medications in PCI patients is associated with lower regional rates of PCI.

**Methods and Results**—Using CathPCI Registry and Dartmouth Atlas data, we examined patients undergoing elective PCI for stable coronary artery disease from January 1, 2009, through March 31, 2011, and calculated rates of providing ≥2 antianginal medicines before PCI. We regressed the hospital referral region rates of PCI per 1000 Medicare enrollees in 2007 on the regions’ rates of providing ≥2 antianginal medications before PCI. Among 300772 PCI procedures, 32.8%, 48.3%, 16.1%, and 2.8% of patients were on 0, 1, 2, or ≥3 antianginal medications, respectively. The median rate of providing ≥2 antianginal medications before PCI was 18.9%. Although substantial variability existed across hospital referral regions in providing ≥2 antianginal medications and in rates of PCI from the Dartmouth Atlas, there was no association between the rates of PCI in each hospital referral region and the rates of ≥2 antianginal medications before PCI (Spearman ρ, 0.0277; P=0.64).

**Conclusions**—We found no association between the intensity of antianginal therapy and the use of PCI across hospital referral regions, despite the variability of both. Opportunities likely exist in many regions to increase the use of antianginal therapy before proceeding to elective PCI, and more research is needed to explain observed variations in care. *(Circ Cardiovasc Interv. 2013;6:436-443.)*

Key Words: angina, stable ■ angioplasty ■ coronary disease ■ stents

**Pharmacology**

Clinical studies in patients with stable coronary artery disease (CAD) without acute coronary syndrome comparing medical therapy alone or in conjunction with percutaneous coronary intervention (PCI) have demonstrated equal rates of cardiovascular events.1-5 Although PCI provides slightly more angina symptom relief, both intensive medical therapy and PCI are associated with significant improvements in symptoms, and many patients become symptom free with medical therapy alone, avoiding the risks of PCI.6

Appropriate use criteria for coronary revascularization help guide physicians in prospectively evaluating whether the expected benefits of treatment outweigh the risks.5,7 The appropriate use criteria grade revascularization at higher levels of appropriateness if more aggressive antianginal medications (≥2 classes of drugs) are used. An analysis of PCI procedures in the United States showed that suboptimal antianginal therapy was a leading cause of an inappropriate PCI for nonacute indications.8 The importance of aggressive antianginal therapy in managing CAD and the variability in appropriateness across hospitals8 raise the possibility that differences in the intensity of medical management may explain the substantial variations in the use of PCI documented by the Dartmouth Atlas of Cardiovascular Health Care, where a 10-fold difference in overall rates of PCI has been documented.9

To explicitly examine the association of the intensity of medical therapy with geographical variations in PCI rates, we analyzed the antianginal therapy of patients with stable CAD undergoing PCI in the National Cardiovascular Data Registry CathPCI Registry and compared the regional rates of antianginal therapy with rates of PCI in the Dartmouth Atlas.7 We hypothesized that higher regional rates of antianginal medication use in patients undergoing PCI would be associated with lower regional rates of PCI.

**Methods**

**Data Sources**

To test our hypothesis, we used 2 data sources: the CathPCI Registry and the Dartmouth Atlas of Cardiovascular Health Care.9 The CathPCI Registry, sponsored jointly by the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, has been described in previous studies.10-14 In brief,
Antianginal Medications

The following medications used to treat angina in the 2 weeks before PCI were recorded: β-blockers, long-acting nitrates, calcium channel blockers, ranolazine, and other antianginal medications. In addition to the individual medications, we examined the overall intensity of attempted antianginal medical therapy in the 2 weeks before PCI based on the appropriateness criteria, wherein maximal antianginal medical therapy is defined as the use of ≥2 classes of therapies to reduce anginal symptoms. Thus, we analyzed the percentage of patients receiving ≥2 of the classes of antianginal medications in the 2 weeks before PCI: β-blockers, long-acting nitrates, calcium channel blockers, or ranolazine.

Statistical Analysis

The number of antianginal medications and symptom status were compared for patients with and without CVD, and characteristics were compared for patients receiving and not receiving ≥2 antianginal medications. Hospital characteristics were compared by the percent of patients receiving ≥2 antianginal medications at each hospital. Pearson χ² tests were used to compare categorical variables, and Wilcoxon rank-sum tests were used to compare continuous or ordinal variables. HRR rates of PCIs from the Dartmouth Atlas were then regressed on HRR rates of providing ≥2 antianginal medications from the CathPCI Registry. We then performed a series of sensitivity analyses for this regression. Analyses were performed on a population limited to patients with a known prior history of CVD and, separately, on only Medicare patients to more closely match the population in the Dartmouth Atlas. Given that some patients may not have been tried on antianginal medications because they presented without symptoms, an analysis limited to patients presenting with symptoms was performed. To examine lower risk populations, further analyses were performed excluding patients with 3-vessel CAD and a left ventricular ejection fraction of <50%, patients with a high-risk exercise treadmill, echocardiogram, or nuclear stress tests, and the combined low-risk population also limited to symptomatic patients. In addition, to assess for substitution effects of CABG in lieu of PCI, sensitivity analyses were performed with regressions of HRR rates of CABG and of the combined revascularization rates of PCI and CABG per 1000 Medicare enrollees on providing ≥2 antianginal medications. All statistical tests were 2-sided, with a P<0.05 defined as the level of significance. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and Stata 10.1 (StataCorp, College Station, TX).

Results

There were 300,772 PCI procedures in our final study population (Figure 1) from 1164 hospitals in 282 HRRs (92.2% of the total 306 HRRs in the Dartmouth Atlas). The hospitals were mostly private/community hospitals (87.0%), located in urban areas (57.1%), with a mean of 447 beds and with half having graduate medical education programs (50.1%). The median annual hospital PCI volume was 749 cases, with an interquartile range of 454 to 1192 cases.

The antianginal therapy of patients before PCI included β-blockers in 59.4%, with considerably lower use of other antianginal therapies (Table 1). Two of the 3 patients (67.2%) were receiving ≥1 antianginal medication before their procedure, but a third of patients were not tried on any antianginal therapy in the 2 weeks before the procedure, and only 18.9% were receiving ≥2 antianginal medicines. A known prior diagnosis of CVD was present in 67.1% of patients. Among those patients, the rate of receiving ≥2 antianginal medications in the 2 weeks before PCI was 22.4% compared with 11.9% among those patients with no known prior CVD (P<0.0001). Patients receiving ≥2 antianginal medications before the PCI procedure were more symptomatic, older, had more comorbid...
conditions, were more likely to be receiving Medicare, and were less likely to be current or recent smokers. Overall, 57% of patients had a prior stress test, with the majority of the results being positive although not high risk (Table 2). Hospitals that were located in urban compared with rural areas had higher median rates of providing ≥2 antianginal medications before PCI (18.0% versus 12.8%; P<0.0001), and hospitals with graduate medical education programs had higher median rates compared with hospitals without (17.9% versus 14.3%; P<0.0001).

Regional Variation
In examining the rates of providing ≥2 antianginal medications in the 2 weeks before PCI across HRRs (median=18.2%), substantial variation was observed, with a range of 0% to 42.0% and an interquartile range of 0.3% to 36.0% (Figure 2). The median rate of PCI per 1000 Medicare enrollees in 2007 was 9.7 (interquartile range, 4.6–22.5).9 We found no association between the rates of providing ≥2 antianginal medications in the 2 weeks before PCI by HRR and the rates of PCI from the Dartmouth Atlas (Spearman ρ, 0.028; P=0.64; Figure 3).

The sensitivity analyses of performing the regression by limiting the study population to only patients with a prior diagnosis of CVD (Spearman ρ, −0.003; P=0.96), to only Medicare patients (Spearman ρ, 0.022; P=0.71), to only symptomatic patients (Spearman ρ, 0.017; P=0.77), to patients without 3-vessel CAD and a left ventricular ejection fraction of <50% (Spearman ρ, 0.04; P=0.51), to patients without high-risk

Table 1. Anti-ischemia Therapy Before PCI for Patients With and Without a Prior Diagnosis of CVD

<table>
<thead>
<tr>
<th>Total (%)</th>
<th>Patients With Prior Diagnosis of CVD (%)</th>
<th>Patients With No Prior Diagnosis of CVD (%)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>300,772</td>
<td>201,762</td>
<td>99,010</td>
</tr>
<tr>
<td>Presenting with symptoms</td>
<td>209,368 (69.6)</td>
<td>136,741 (67.8)</td>
<td>72,627 (73.4)</td>
</tr>
<tr>
<td>Individual medications*</td>
<td>178,500 (59.4)</td>
<td>134,330 (66.6)</td>
<td>44,170 (44.6)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>47,934 (15.9)</td>
<td>33,736 (16.7)</td>
<td>14,198 (14.3)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>37,593 (12.5)</td>
<td>30,703 (15.2)</td>
<td>6,890 (7.0)</td>
</tr>
<tr>
<td>Long-acting nitrate</td>
<td>4,008 (1.3)</td>
<td>3628 (1.8)</td>
<td>380 (0.4)</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>8229 (2.7)</td>
<td>5802 (2.9)</td>
<td>2,427 (2.5)</td>
</tr>
<tr>
<td>Other antianginal</td>
<td>98,686 (32.8)</td>
<td>52,442 (26.0)</td>
<td>46,244 (46.7)</td>
</tr>
<tr>
<td>No. of antianginal medications†</td>
<td>145,175 (48.3)</td>
<td>104,155 (51.6)</td>
<td>41,020 (41.4)</td>
</tr>
<tr>
<td>Patients receiving ≥2 antianginal therapies before the procedure†</td>
<td>48,355 (16.1)</td>
<td>37,704 (18.7)</td>
<td>10,651 (10.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>8,556 (2.8)</td>
<td>7,461 (3.7)</td>
<td>1,095 (1.1)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; and PCI, percutaneous coronary intervention.
*Antianginal medicines attempted within 2 wk before procedure.
†Summation of the following antianginal medications: β-blockers, calcium channel blockers, long-acting nitrates, and ranolazine.
‡P value for all comparisons of patients with prior diagnosis of CVD to patients with no prior diagnosis of CVD.
stress tests (Spearman $\rho$, 0.028; $P=0.64$), and to symptomatic patients without high-risk features or stress tests (Spearman $\rho$, 0.027; $P=0.66$) yielded similar results. Furthermore, when performing a regression of CABG rates on providing ≥2 antianginal medications (Spearman $\rho$, 0.064; $P=0.28$) and total revascularization (PCI and CABG) on providing ≥2 antianginal medications (Spearman $\rho$, 0.053; $P=0.38$), again there was no correlation between rates of antianginal therapies and revascularization.

Of the 282 HRRs examined, there were 68 HRRs (24.1%) with below-median rates of both providing ≥2 antianginal medications and PCI, 73 HRRs (25.9%) with below-median rates of providing ≥2 antianginal medications but above-median PCI rates, 68 HRRs (24.1%) with higher than median PCI rates, and 73 HRRs (25.9%) with higher than median rates of ≥2 antianginal medications but below-median PCI rates.

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rates of both providing ≥2 antianginal medications and PCI, and 73 HRRs (25.9%) with higher than median rates of providing ≥2 antianginal medications but below-median PCI rates (Figure 3). As examples, 1 HRR had a particularly high rate of providing ≥2 antianginal medications (42.0%) with a low rate of PCI (5.7), another HRR had the opposite relationship with a low rate of providing ≥2 antianginal medications (9.0%) and a high rate of PCI (20.5), and yet a third had high rates of both providing ≥2 antianginal medications (22.5%) and PCI (26.8).

**Discussion**

Using 2 large national databases on the care of patients with CAD, our study found substantial variation in the intensity of antianginal therapy before PCI for stable CAD and a low overall use of ≥2 antianginal medications. Importantly, there was no association between the rates of providing ≥2 antianginal medications in the 2 weeks before PCI and the rates of PCI. A large percentage of patients were receiving β-blockers, yet <1 in 5 had the comprehensive antianginal therapy recommended by the revascularization appropriate use criteria attempted in the 2 weeks before PCI. Although our database did not collect information on contraindications to antianginal therapies, thereby limiting our ability to assess overall attempts at antianginal therapy, there is no logical reason to think that patient characteristics restricting use of antianginal therapies would vary from region to region. Furthermore, the substantial variation in providing ≥2 antianginal medications across HRRs suggests that there may be regional practice patterns that are associated with providing high levels of medical therapy. The lack of correlation between the rates of antianginal therapy and PCI suggests that other variables, besides medical therapy, explain the variability in rates of PCI. However, more than a quarter of regions provided both high levels of...
antianginal therapy for patients with stable CAD and low rates of PCI, suggesting that the practice patterns of these regions may provide insights into strategies that seem to preferentially reserve PCI for patients who fail medical therapy.

The multicenter Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial demonstrated that optimal medical therapy was highly effective in reducing anginal symptoms and in delaying or preventing the need for PCI. Building on these findings, the appropriate use criteria recommend that, in determining the need for revascularization for stable CAD, physicians assess symptoms, coronary anatomy, results of noninvasive stress testing, and the degree of antianginal therapy. Our finding of the low rate of antianginal therapy in patients undergoing PCI, even with the understanding that contraindications were not recorded, is congruent with work examining the appropriate use criteria, wherein 95.8% of patients who underwent inappropriate PCI were on ≤1 antianginal therapies. More than 2 of 3 patients in our study had been diagnosed with CVD before their PCI and while better than the 11.9% rate of providing ≥2 antianginal medications for patients with no prior diagnosis of CVD, the rate among these patients with known CVD was just slightly >20%. Collectively, the low rates in providing ≥2 antianginal medications before PCI suggest an important opportunity to ensure that maximal medical therapy is attempted before proceeding to PCI. Although the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial demonstrated that ischemia-driven revascularization for stable CAD led to fewer urgent revascularizations, multiple studies have shown no benefit of PCI for stable CAD on myocardial infarction or mortality. The presumed main reason for PCI continues to be relief of symptoms, and the decision to perform PCI should ideally occur after a trial of medical therapy has been proven to be ineffective in controlling patients’ symptoms.

In contrast to our hypothesis that more aggressive use of antianginal medications would be associated with lower rates of PCI in HRRs, we found that the regional rates of antianginal therapies were unrelated to rates of PCI. Extensive work by the Dartmouth Atlas group has demonstrated regional variations in healthcare, dating back to 1973. No clear and consistent explanation has yet been found for these variations in practice patterns, which have been presumed to be driven by physician preferences. Similarly, we found that our hypothesis that antianginal medication use would explain the variation in PCI rates was, in fact, not the answer. It seems that the factors driving technological utilization, such as PCI, are more complex than any 1 element.

Previous studies have examined biological factors, health system determinants, local marketplace elements, supply-sensitive care, and patient preferences as drivers of variation. For example, Zuckerman et al have suggested that patients’ health status, which was not quantified in our study, accounted for 29% of regional variability in expenditures. Similarly, studies of structural features of various health systems have found that national healthcare policies and fragmentation of care also contribute to differing rates of healthcare utilization. On a smaller scale, differences in local economic conditions within a region have also been posited as causes for variations in healthcare utilization; however, adjusting Medicare spending for the cost of goods and services in individual economic areas only explains a small amount of observed variation in medical utilization. Supporting the possibility that variations in use are because of an excess supply of providers, previous studies have demonstrated that an increased availability of cardiac hospitals and diagnostic testing is associated with greater rates of revascularization. Interestingly, studies examining links between supplies of cardiologists and implantable cardioverter-defibrillators and between supplies of back surgeons and lumbar procedures did not find similar results, thus belying a consistent answer. Although patient preferences could drive some of the observed variation in care, such preferences previously have been shown not to vary substantially from region to region as a way of explaining differences in resource utilization. Our data add to these studies by providing a more nuanced portrait of the variations in care for patients with stable CAD and by demonstrating that the intensity of antianginal therapy does not explain the observed differences in care.

Although we did not find an overall association of antianginal therapy and utilization of PCI, it is important to note that the regions are spread through all 4 quadrants of providing higher and lower levels of both medical therapy and revascularization. There are regions that have high rates of medical therapy and low rates of PCI, perhaps confirming our hypothesis in those regions that by receiving antianginal therapy, those patients avoid the need for elective PCI. However, there are also regions that, despite providing high degrees of medical therapy, still have high rates of PCI for these patients with stable CAD. One possibility is that these regions are providing more healthcare overall: they aggressively apply antianginal therapy, follow their patients intensively, and also perform PCI perhaps for angina detected by the close follow-up and made more appropriate by the higher degree of medical therapy. Qualitative analyses, such as with physician surveys and interviews, of the factors unique to hospitals in these 4 quadrants of antianginal therapy and PCI may help explain the relationship between medical therapy and the rates of PCI. In particular, such studies should examine variables, such as physician knowledge and attitudes toward relevant clinical trials, and local and regional health system factors. It is likely that the relationship between antianginal therapy and PCI is multifactorial. By examining the interaction between various elements that have previously been studied independently, the medical community can more fully understand variations in care.

Limitations
Our findings should be interpreted within the context of several potential limitations. First, we used data from 2 different populations that were collected at different times. Our study population in the CathPCI Registry included patients of all ages undergoing elective PCI for stable CAD in 2009 to 2011. The Dartmouth Atlas data included Medicare beneficiaries who were generally >65 years of age and were undergoing PCI for both acute and nonacute indication in the year 2007. Nonetheless, limiting the CathPCI Registry data to include only Medicare patients resulted in similar findings, and the correlations aggregated at the regional level should be relevant, because
there is no clinical reason to think that proportions of acute PCIs would vary by HRR. Prior work has shown that practice patterns within an HRR remain relatively constant over time (so-called surgical signature). A second potential limitation is that there may be differences in the representativeness of CathPCI Registry sites with HRRs. The construction of HRRs stem from care received at tertiary medical centers for major cardiovascular surgical and neurosurgical care. Because PCI is often performed at cardiac surgery hospitals, there is good reason to believe that the CathPCI Registry sites correlate with HRRs. We did have a substantial coverage in the United States of HRRs with, even after excluding regions with <50 PCIs, HRRs. We did have a substantial coverage in the United States with no correlation to the rates of PCI, yet a significant proportion of regions provided both high degrees of angiography and PCI with or without PCI for stable coronary disease. N Engl J Med. 2005;353:1503–1516.

A third consideration is that the CathPCI Registry does not contain information on contraindications to antiangiinal therapy, such as symptomatic intolerance to long-acting nitrates or bradycardia with β-blockers. Nor does the Registry track dosages, duration of therapy, or indicators of therapy effectiveness, such as heart rate response to β-blockers. However, the Registry does record whether any of the antiangiinal medications were tried in the prior 2 weeks, tolerated or not tolerated, and at any dose and for any duration. Thus, although we cannot comment on the overall delivery of antiangiinal therapy accounting for contraindications, there is no clear reason for systematic biases across HRRs in patients having contraindications. Furthermore, the bias introduced by this limitation may also be to credit the patient as having received an antiangiinal therapy, even if it had not been given enough of a trial to control patients’ symptoms.

Fourth, although we found that patients receiving ≥2 antiangiinal medications had more comorbidities because many of the antiangiinal medications simultaneously treat conditions such as hypertension, the comorbidities should not be expected to vary substantially by region. Thus, we may have overestimated the use of these medications for antiangiinal indications. A small percentage of patients were on other antiangiinal medications for which we do not have data; however, this total of 2.7% of patients is unlikely to change the primary study findings. In addition, although our sensitivity analysis identifying a low-risk population that may have been driven by clinical factors, regardless of symptoms and antiangiinal therapy. Finally, we cannot know from our data the degree to which patients treated noninvasively received antiangiinal therapy. However, these data would not alter the finding that, among patients undergoing elective PCI, the degree of antiangiinal medical therapy was not associated with regional rates of PCI.

Conclusions
In conclusion, our study demonstrates that many patients undergoing elective PCI for stable CAD have not been tried on ≥2 antiangiinal medications in the 2 weeks before PCI. The rates of antiangiinal medications varied widely across the United States with no correlation to the rates of PCI, yet a significant proportion of regions provided both high degrees of antiangiinal therapy and lower rates of PCI, suggesting that understanding these practice patterns could provide insights into higher-quality healthcare.

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Disclosures
Dr Borden is currently a senior advisor in the US Department of Health and Human Services. His work on this study was conducted through Cornell University and is not related to the Department of Health and Human Services. The financial disclosures for Dr Roe are listed at www.dcri.org. Dr Redberg is a Medicare Payment Advisory Commissioner and member of the Medicare Evidence Development and Coverage Advisory Committee, but this study was performed independently of that work. The other authors report no conflicts.

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